CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213801Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Brief Memo

<table>
<tr><td>Date</td><td>March 24, 2021</td></tr>
<tr><td>From</td><td>Mark S. Hirsch, M.D.</td></tr>
<tr><td>Subject</td><td>Cross-Discipline Team Leader (CDTL) Brief Memo</td></tr>
<tr><td>NDA/BLA#
/Supplement#</td><td>NDA 202611 S-017
NDA 213801</td></tr>
<tr><td>Applicant</td><td>Astellas Pharma US, Inc.</td></tr>
<tr><td>Date of Submission</td><td>September 28, 2020</td></tr>
<tr><td>PDUFA Goal Date</td><td>March 26, 2021</td></tr>
<tr><td>Proprietary Name / Established (USAN) names</td><td>Myrbetriq (mirabegron extended-release tablets)
Myrbetriq Granules (mirabegeron extended-release granules for oral suspensión)</td></tr>
<tr><td>Dosage forms / Strengths</td><td>Myrbetriq: Starting dose: 25 mg once daily. May increase to 50 mg once daily after 4 to 8 weeks.

Myrbetriq Granules: See table for once daily starting dose. May increase to lowest effective once daily dose after 4 to 8 weeks.
<table>
<tr><th>Body Weight</th><th>Starting Dose</th><th>Maximum Dose</th></tr>
<tr><td>11 kg to less than 22 kg</td><td>3 mL (24 mg)</td><td>6 mL (48 mg)</td></tr>
<tr><td>22 kg to less than 35 kg</td><td>4 mL (32 mg)</td><td>8 mL (64 mg)</td></tr>
<tr><td>Greater than or equal to 35 kg</td><td>6 mL (48 mg)</td><td>10 mL (80 mg)</td></tr>
</table></td></tr>
<tr><td>Indication(s)</td><td>Myrbetriq: Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older and weighing 35 kilograms or more
Myrbetriq Granules: Treatment of NDO in pediatric patients aged 3 years and older</td></tr>
<tr><td>Recommended:</td><td>Approval</td></tr>
</table>

The purpose of this CDTL Brief Memo Update is:

1) To confirm my agreement with the review teams' recommendations for Approval of these applications,

2) To provide brief summaries of the discipline-specific and consultative reviews, and

3) To confirm my agreement with the final labeling for these NDAs.

1. Confirm CDTL Recommendation for Approval

CDTL Note: For full CDTL conclusions on benefits and risks of Myrbetriq and Myrbetriq Granules for treatment of NDO in pediatric patients, the reader is referred to the final Clinical Review dated March 18, 2021, under the heading "Benefit-Risk Assessment" (Section 1.3). Here, I briefly summarize conclusions on the product's benefits and risks

and confirm my agreement with the teams' regulatory decisions to approve these applications.

Background
Mirabegron is a selective beta-3 adrenergic receptor agonist. Activation of beta-3 adrenergic receptors that reside on bladder smooth muscle causes relaxation of bladder smooth muscle inhibition of involuntary detrusor muscle contractions, and increased bladder capacity. Mirabegron is currently approved as Myrbetriq 25 mg and 50 mg mirabegron extended-release tablets for the treatment of overactive bladder (OAB) in adults. The Sponsor now provides data concerning the safety and efficacy of mirabegron for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older. NDO is defined as detrusor overactivity that occurs as a result of a known neurologic lesion, such as congenital myelomeningocele (spina bifida) or spinal cord injury. The goal of therapy in pediatric NDO is to preserve renal function and to minimize symptoms of detrusor overactivity by increasing bladder capacity. The clinical studies that support these applications investigated the approved Myrbetriq tablets (mirabegron extended-release tablets) and also a new mirabegron formulation, Myrbetriq Granules (mirabegron extended-release granules for oral suspension). Myrbetriq tablets are considered appropriate for children weighing 35 kg or more. Mybretriq Granules, the new oral suspension, facilitates swallowing for younger children and allows more accurate dose titration.

Efficacy
The efficacy of Myrbetriq and Myrbetriq Granules was demonstrated in the phase 3 study 178-CL-206A, an open-label, baseline-controlled, multicenter, dose-titration study in 86 pediatric patients aged 3 to < 18 years with NDO who had been practicing continuous intermittent catheterization (CIC). The study included a 24-week, dose-titration period followed by a 28-week, fixed-dose period. As previously mentioned, two dosage forms were studied: Myrbetriq (in patients ≥ 35 kg), and Myrbetriq Granules (in patients < 35 kg, and patients ≥35g who could not, or who preferred not, to take tablets). The study demonstrated clinically meaningful increases in maximum cystometric capacity, the primary efficacy endpoint, as well as improvements in the secondary efficacy endpoint, that included other urodynamic parameters and e-diary recorded bladder volume and urinary leakage measurements. The magnitude of treatment effect was similar across age groups.

Safety
The safety of Myrbetriq and Myrbetriq Granules was assessed in a total of 86 pediatric patients with NDO. Overall, the safety profile of mirabegron in pediatric patients with NDO was consistent with its safety profile in the treatment of adults with OAB. In the 52-week study 178-CL-206A, there were no deaths and no drug-related SAEs. Discontinuations due to AEs were few (n=3) and none were determined to be study drug related. The most commonly reported adverse reactions were UTI (24.4%, which includes E.coli UTI, UTI bacterial, UTI, and UTI Pseudomonal), nasopharyngitis (5.8%), constipation (4.7%), and headache (3.5%). The high incidence of UTI events was thought to reflect, at least in part, the high incidence of UTI in pediatric NDO patients practicing CIC. AEs of special interest, also determined to be not drug related, included: bradycardia, QT prolongation, neoplasm, and seizure, each reported in a single patient; hypersensitivity reactions (n=5); and fetal disorder after exposure during

pregnancy (n=1), which was erroneously coded. Vital signs assessment showed a mean increase from baseline in blood pressure (BP) of 4.3 mm Hg systolic and 1.7 mm Hg diastolic for patients less than 12 years of age. Larger BP increases were observed in patients less than 8 years of age. The increases in BP did not appear to increase with mirabegron exposure. Finally, postmarketing AE cases were either confounded by comorbid conditions and concomitant medications or lacked key clinical information.

Risk: Benefit
From an overall risk: benefit perspective, mirabegron tablets and oral suspension are efficacious, have an acceptable safety profile consistent with the safety profile in adults, and provide an alternative treatment option for pediatric patients with NDO. Mirabegron tablets and oral suspension are a once-daily dosing regimen, and the data support safety and efficacy for patients as young as 3 years. The benefits compare favorably against the risks, which are similar to, and consistent with, the known risks in adults with OAB. The clinical studies of mirabegron tablets and oral suspension in pediatric patients with NDO identified no safety signals beyond those already known for mirabegron tablets in adults with OAB. Labelling is adequate to address the known risks.

I confirm my agreement with the review team that the applications for Myrbetriq and Myrbetriq Granules for the treatment of NDO in patients 3 years of age and older should be Approved.

2. Brief Summaries of the Discipline-Specific and Consultative FDA Reviews

CDTL Note: For additional details on the discipline-specific and consultative reviews completed through May 18,2020, the reader is referred to the final Clinical Review dated March 18, 2021, under "Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety." The reader is also referred to the final discipline-specific reviews themselves. Here, I summarize the recently completed discipline-specific and consultative reviews.

2.1 Chemistry

In the final Integrated Quality Assessment (IQA), dated March 24, 2021, the ***Chemistry*** (OPQ) team of Sam Bain, Donna Christner, Mark Seggel, Wendy Wilson-Lee, Yong Wu, Yubing Tang, Jason God, Julie Nemecek, Assadollah Noory, Vidula Kolhatkar, and Hong Cai had the following Recommendation and Conclusion:

"Astellas Pharmaceuticals' 505(b)(2) New Drug Application 213801, for MYRBETRIQ Granules (mirabegron for extended-release oral suspension), 8 mg/mL of mirabegron after reconstitution, is recommended for APPROVAL from the OPQ perspective.

Sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, and bioavailability of the drug product.

The prescribing information (PI) and patient package insert (PPI) as submitted March 23, 2021 (0036) and March 19, 2021 (0037) are accurate, complete and comply with the requirements under 21 CFR 201.

All drug substance and product-related manufacturing, packaging and testing facilities have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on March 17, 2021. The recommendation remains current as of this review.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable."

From the Chemistry review, the following is also notable:

- The maximum use-period after Myrbetriq Granules are reconstituted with water is 28 days at room temperature. This information was incorporated into labeling.

- The dissolution rate of mirabegron from Myrbetriq Granules when alcohol is added (alcohol dose-dumping study) is increased. The addition of alcohol (5, 10, 20, and 40%) increased the dissolution rate of mirabegron from Myrbetriq granules at pH 6.8. This information was incorporated into labeling.

2.2 Division of Biometrics III (DB3)

In their final ***Statistical*** review dated March 11, 2021, Jia Guo and Daphne Lin had the following Conclusion:

"*…Based on reviewer's analyses, the submitted study demonstrated clinical benefit for this indication in pediatric patients…The study demonstrated that there is clinical benefit of mirabegron in treatment of NDO in pediatric subjects".*

2.3 Clinical

In our final ***Clinical*** review dated May 18, 2020, Elena Boley and I had the following Conclusion:

"*At this time, the Clinical review team recommends that this NDA and sNDA should be APPROVED".*

In regard to efficacy, safety and risk: benefit analysis, the Clinical team concluded:

- "*From the Clinical perspective, the evidence presented in this NDA and sNDA is adequate to support the effectiveness of this product in the treatment of pediatric patients with NDO."*

- "*The safety profile of mirabegron tablets and oral suspension is consistent with the known risks of mirabegron tablets for the treatment of OAB in adults*".

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